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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/817,950	03/27/2001	Paul M. Guyre	DC-0153	4097

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EXAMINER	
BELYAVSKYI, MICHAIL A	
ART UNIT	PAPER NUMBER
1644	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/23/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/817,950	GUYRE ET AL.	
	Examiner	Art Unit	
	Michail A. Belyavskyi	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 December 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11 and 12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11 and 12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1 Applicant's amendment, filed 12/07/06 is acknowledged.

Claims 11 and 12 are pending.

In view of the amendment filed 12/07/06 the following rejection remains:

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 11 and 12 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Coligan et al. (Current Protocols in Immunology, Greene Publishing Associates and Wiley-Interscience, New York, 1991; pages 2.1.1-2.1.3, 2.1.9-2.1.11, and 2.1.17-2.1.22) in view of U.S. Patent 5,077,216, Zwadlo et al (IDS Reference BA) Zwadlo et al (IDS Reference AX) , Hogger et al(Pharmaceutical Research, 1998, Vol.15, pages 296-302) and Droste et al., (Biochem and Biophys. Res. Comm, 1999, Vol. 256, pages 110-113) as is evidenced by Sulahian et al (Cytokine, 2000, Vol.12, pages 1312-1321) for the same reasons set forth in the previous Office Action, mailed on 09/21/06.

Applicant's arguments filed 12/07/06 have been fully considered but they are not persuasive.

Applicant asserts that : (i) none of the references teach that cell surface expression of CD163 correlates in any way with CD163 levels shed in vivo; (ii) while Droste et al., teach shedding of CD163 in vitro, said reference does not teach that CD163 is shed in vivo in patient exposed to an inflammatory stimulus; (iii) As evidence by the teaching of Kubo et al., the prior art indicates that *in vitro* shedding experiments are not wholly indicative of *in vivo* solubilization of proteins

Applicants have traversed the primary and the secondary references pointing to the differences between the claims and the disclosure in each reference. Applicant is respectfully reminded that the rejection is under 35 USC103 and that unobviousness cannot be established by attacking the references individually when the rejection is based on the combination of the references. see In re Keller, 642 F.2d 4B, 208 USPQ 871, 882 (CCPA 1981) See MPEP 2145. This applicant has not done, but rather argues the references individually and not their combination. One cannot show non-obviousness by attacking references individually where the rejections are based on a combination of references. In re Young 403 F.2d 759, 150 USPQ 725 (CCPA 1968).

Coligan et al., teach an antibody-sandwich ELISA to detect soluble antigens, which is the most useful of the immunosorbent assays for detecting antigen because it is very sensitive (see page 2.1.9 in particular), plates are coated with a specific capture antibody, test samples added, and soluble antigens are detected with another antibody. A developing reagent is adted to detect antibody/antigen complexes (see page 2.1.0 in particular). Coligan et al. teach that ELISAS are useful for screening biological fluids (e.g. from plasma) for antigen content (see page 2.1.20, left column in particular).

Coligan et al. do not teach a method for detecting an early signaling event in an inflammatory response, comprising detecting CD163 with antibodies directed against CD163, wherein said antibody is monoclonal antibodies MAC2-158, or MAC2-48 and wherein CD163 is soluble CD163.

The US Patent '216 teaches a method of detecting a p155 human mononuclear phagocyte-specific antigen using the monoclonal antibodies MAC2-158 and MAC2-48 (see columns 1, 7, 12, ant the claims in particular). The monocytes detected were obtained from human plasma (see column 5, paragraphs 1-2 in particular).

Zwaldo et al. (IDS Reference BA) teach that RM3/1 antigen (.i.e. CD161 antigen) is useful for monitoring an early signaling event in an inflammatory response in a patient. The examiner disagree with Applicant interpretation that Zwadlo et al. teaches away from the present invention in teaching that the RM3/1 antigen (i.e. CD163) is appearing late in the inflammatory response. Zwaldo et al. teach that the levels of RM3/1 antigen (i.e. CD163) reached a maximum levels late in the inflammatory response. However, Applicants attention is drawn to pages 299, 301 and 303, wherein Zwaldo et al. explicitly teach that depending on the stage of inflammation RM3/1 antigen is expressed at different levels. Zwaldo et al. explicitly teach that in acute inflammation , i.e. early in an inflammatory response, RM3/1 antigen expressed to varying degree, depending on the stage of inflammation. In addition, Zwaldo et al. ., (IDS

Reference AX teach to monitor the appearance of RM3/1 positive macrophages in blood between 24 and 72 hr post inflammatory response (see abstract in particular).

It would be immediately obvious to one skill in the art that Zwaldo et al., teach that detection of the expression of RM3/1, i.e. CD163 is useful for monitoring an early signaling event in an inflammatory response. Moreover, as is evidenced by Sulahian et al., based on the teaching of Zwaldo et al., it has been suggested that CD163 bright macrophages play a role in the resolution of inflammation as they are found in the high numbers in inflammation tissues. It is noted that applicants are co-authors of Sulahian et al., reference.

Hogger et al., teach that injection of glucocorticoids into primates or human volunteers results in an increase of RM3/1 positive blood monocytes within 6 hr. Hogger et al., also teach that monocytes expressing RM3/1 antigen i.e. CD163, are also present in acute inflammation (see entire document, page 296 in particular). Hogger et al., teach that the level of expression of RM3/1 antigen i.e. CD163, can be measured by antibody labeling and subsequent FACS analysis (see page 302 in particular). In other words, it would be immediately obvious to one skill in the art that Hogger et al., teach that expression of RM3/1 antigen i.e. CD163 is an indicative of an early signaling event in the inflammatory response.

Droste et al., teach that CD163 is a member of the scavenger receptor family which expressed on human monocytes and macrophages. Upon an inflammatory stimulus this protein is shed rapidly from the cell membrane and exists as a soluble protein (see entire document, Abstract and Fig. 2 in particular). In other words one skill in the art would understand that that the appearance of soluble form of CD163 is an the indicative of the inflammatory response cascade.

With regards to Applicant's comments that none of the references teach that cell surface expression of CD163 correlates in any way with CD163 levels shed in vivo; and while Droste et al., teach shedding of CD163 *in vitro*, said reference does not teach that CD163 is shed *in vivo* in patient exposed to an inflammatory stimulus.

Specific statements in the references themselves which would spell out the claimed invention are not necessary to show obviousness, since questions of obviousness involves not only what references expressly teach, but what they would collectively suggest to one of ordinary skill in the art. See CTS Com. v. Electro Materials Corp. of America 202 USPQ 22 (DC SINY); and In re Burckel 201 USPQ 67 (CCPA).

The examiner disagrees with Applicant's interpretation of Droste et al reference. It is the examiner position that based on the teaching of Droste et al., one skill in the art would expect that the inflammatory stimulus induces shedding of CD163 from monocytes in vivo. Moreover, Applicants position is further supported by the disclosure of the instant Specification. At page 10, lines 20-25, the Specification clearly disclosed that **in order to more closely mimic the in vivo inflammatory response to infection** in a more controlled setting, healty volunteers were administered LPS and monitored the levels of soluble CD163 in plasma. As disclosed in the prior

art of Droste et al, LPS has been shown to induce shedding of CD163 from monocytes *in vitro* (emphases added) . In other words, the Specification teaches that it would be obvious to one skill in the art that LPS-induced shedding of CD163 *in vitro* correlates with LPS-induced shedding of CD163 *in vivo*

With regards to Applicant's comments that as evidence by the teaching of Kubo et al., the prior art indicates that *in vitro* shedding experiments are not wholly indicative of *in vivo* solubilization of proteins.

The examiner disagrees with Applicant's interpretation of Kubo et al., reference. Applicant's attention is respectively drawn to page 273, right column. Kubo et al., teach that **shedding of L-selectin did occur *in vitro* at concentration comparable or less than those occurring *in vivo*** (emphases added). It is the examiner position that one skill in the art would interpret Kubo et al., reference as teaching that the *in vitro* shedding experiments are indeed an indicative of *in vivo* shedding .

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the MAC2-158 or MAC2-48 antibodies as capture antibodies taught by the '216 patent and the antibodies taught by Zwaldo et al., as the detection antibody in the ELISA assay taught by Coligan et al. to have a method for monitoring the course of an inflammatory condition or inflammatory response in a patient by detecting the levels of soluble CD163 in the biological sample as taught by combine references of Zwaldo , Hogger et al. and Droste et al.

One of ordinary skill in the art would have been motivated to use the antibodies taught by the '216 patent and Zwaldo et al. in the ELISA taught by Coligan et al. because to detect and monitor the presence of CD163 in a biological sample, such as human plasma, during an early inflammatory condition/process, such as rheumatoid arthritis by detecting CD163 (i.e. RM3/1 antigen) as taught by Zwaldo et al and Hogger et al.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, because CD163 is shedding rapidly upon inflammatory stimulus, and thus can be an the indicative of the inflammatory response cascade as taught by Droste et al. Detecting soluble CD163 levels can be used to monitor an early inflammatory response cascade in the patient, as taught by Zwaldo et al and Hogger et al. CD163 levels in biological sample can be detected using the antibodies taught by the '216 patent and Zwaldo et al. in the ELISA taught by Coligan et al.
From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

4. No claim is allowed.

5. **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is 571/272-0840. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571/272-0841.

The fax number for the organization where this application or proceeding is assigned is 571/273-8300

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MICHAIL BELYAVSKYI, PH.D.
PATENT EXAMINER

2/16/07